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The role of the delta neutrophil index in predicting 28-day mortality and thrombolytic treatment indications in pulmonary embolism

Adil Emre Gezer[1], Fatih Ahmet Kahraman[2], Melih Çamcı[2]
[1] Department of Emergency Medicine, Pursaklar State Hospital
[2] Department of Emergency Medicine, Ankara City Hospital, Ankara Yıldırım Beyazıt University, Ankara, Turkey

Abstract
Aim: The aim of this study is to determine whether delta neutrophil index (DNI) values have an effect on predicting 28-day mortality and thrombolytic indications in patients with pulmonary embolism (PE).
Material and Methods: In our study, the age, gender, history of chronic diseases, the laboratory findings (WBC, RDW, DNI, Urea, Creatinine, pH, Lactate), the localization of the pulmonary embolus/emboli, the observed symptoms, whether the thrombolytic therapy was given in the emergency room, 28-day mortality status of 311 patients who were diagnosed with PE in the emergency department and met the inclusion criteria, were recorded and analyzed.
Results: A significant difference was found in the age distribution of the evaluated patients who survived and died in the 28-day follow-up period. When the biochemical parameters were evaluated according to the presence of 28-day mortality, WBC, NEU, LYM, LYM%, EOS, RBC, HGB, RDW, DNI, Urea, D-dimer, Troponin and CRP were found to be statistically significantly different between the two groups. It was found that as the DNI value increased, there was an increase in the 28-day mortality rate.
Discussion: An increase in DNI, especially in the inflammatory processes, suggests that it will also increase during PE. DNI values obtained as part of a complete blood count can be easily estimated without an additional cost or a time burden. We predict that an increased DNI value is useful as a marker in estimating 28-day mortality in patients with acute PE, a disease with high mortality and morbidity.

Keywords
Pulmonary Embolism, Emergency Department, Delta Neutrophil Index (DNI), Mortality

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Corresponding Author: Melih Çamcı, Üniversiteler Mahallesi, 1604. Cadde, No: 9, Çankaya, Ankara, Turkey.
E-mail: melih112_@hotmail.com P: +90 505 883 91 81
Corresponding Author ORCID ID: https://orcid.org/0000-0003-4797-0816

Introduction

By definition, a pulmonary embolism (PE) occurs when the pulmonary artery or one of its branches is blocked by a thrombus or non-thrombotic substances (fat, air, amniotic fluid, etc.) formed elsewhere in the body and is a life-threatening clinical condition when an emergency diagnosis is not made. Pulmonary embolism develops in 90% of cases due to a piece of thrombus ruptured from the deep veins of the lower extremities. The picture in which PTE and DVT are seen together is named a venous thromboembolism (VTE). The mean annual incidence of venous thromboembolism (VTE) is between 39-115/100,000. The risk of venous thromboembolism increases with age. Its incidence is equal in both sexes [1,2]. However, studies conducted in the United States of America have shown that pulmonary embolism is 25% more fatal in men [3]. Mortality from PTE decreases from approximately 25-30% to 2-8% in the treated cases in contrast to the untreated cases [4]. Shortness of breath, tachypnea, tachycardia and chest pain are common symptoms and physical examination findings in patients with pulmonary embolism. However, it should be noted that these signs and symptoms are not peculiar to PE. Pleuritic chest pain with shortness of breath and tachypnea is present in more than 50% of the cases. Hemoptysis occurs in 10% of the cases [5]. PE patients are clinically classified as "low, moderate and high probability" by a scoring made according to their signs, symptoms and risk factors. The combined use of D-dimer and clinical scoring allows the diagnosis to be excluded without further investigation in approximately 30% of patients with suspected PTE [6,7]. The Wells scoring and modified Geneva scoring are commonly used scoring methods [8]. Hypoxemia, hypocapnia and respiratory alkalosis are detected in arterial blood gases (ABG) of patients with PE. High levels of D-dimer do not always give the diagnosis of PE. A negative D-Dimer can be used to exclude PE in patients with no comorbidity and with an estimated low and moderate clinical probability [9,10]. Increased serum troponin level during PE indicates a right ventricular dysfunction. Increased cTnT was found to be associated with early mortality. It has been reported that an elevated Brain Natriuretic Peptide is also associated with right ventricular dysfunction and early mortality [11,12]. Differentiating a patient diagnosed with PE as high-risk (massive), medium-risk (submassive) or low- risk (nonmassive) is important in terms of determining treatment options (anticoagulant/thrombolysis), prognosis and early mortality risk. In patients presenting to the emergency department with symptoms of shock and hypotension, thrombolytic therapy can be given to those who developed PE before the operation. Streptokinase, urokinase and recombinant tissue plasminogen activator (rt-PA) are used as thrombolytic agents [13].

Delta neutrophil index (DNI) is defined as immature granulocytes not found in peripheral blood. It is the common name of myelocytes, promyelocytes and metamyelocytes, that is, granulocyte (neutrophil) precursors found in the bone marrow. DNI is a marker showing the number of immature granulocytes and is calculated by dividing the number of immature neutrophils circulating in the peripheral blood by the total number of neutrophils [14]. In a limited number of studies, the delta neutrophil index was used in patient groups in which inflammatory processes such as sepsis, acute appendicitis, meningitis, decompensated heart failure, acute gout attack, and acute pancreatitis were at the forefront and was thought that it could be a guide in determining the disease severity [15]. The increase in DNI in PE due to vascular inflammation in the pulmonary arteries suggested that we can obtain some guiding results. The aim of our study is to show whether DNI values have an effect on 28-day mortality and has an effect on foreseeing the thrombolytic indication in these patients.

Material and Methods

The present study is a retrospective, observational study. After obtaining the approval from the Ankara City Hospital Clinical Research Ethics Committee dated 30/04/2020 and numbered E1-20-490, patients who came to the Ankara City Hospital Emergency Medicine Clinic between 15.03.2019 and 15.08.2020 were enrolled in the study.

Criteria for inclusion in the study:

1. More than 18 years of age
2. Patients with confirmed pulmonary embolism through Thoracic CT-angiography
3. Patients who received thrombolytic therapy in the emergency department

Criteria for exclusion from the study:

1. Age under 18 years
2. Patients with chronic pulmonary embolism
3. Those with chronic inflammation
4. Patients whose information in the retrospective study form could not be accessed
5. Patients with a diagnosis of sepsis
6. Those with hematological malignancies
7. Those who received chemotherapy within 7 days before reporting to the emergency room
8. Those referred to other hospitals
9. Those who left the hospital by signing a refusal form of treatment despite medical advice

A total of 503 patients were evaluated whose computed thoracic angiography taken in our emergency department was reported by the radiology clinic and consulted by the pulmonology clinic with the diagnosis of pulmonary embolism. Since 21 of these patients had chronic pulmonary embolism, 13 patients had hematological malignancies, 69 patients' hospitalization, mortality status and telephone numbers could not be determined, blood tests of 61 patients were missing / incomplete/data on the device could not be sent to the system, 28 patients' CTA reports were not available in the system, they could not be included in the study. A total of 192 patients were excluded from the study. As a result, 311 patients were included in the study. Demographic characteristics of 311 patients, complaints on admission, vital signs, chronic diseases, laboratory and imaging results, 28-day mortality status, whether thrombolytic treatment was given in the emergency room and DNI, which is studied by the fully automatic blood count analyzer Advia2120 (Siemens Healthcare Diagnostics, Forchheim, Germany) in the emergency laboratory of our hospital and is automatically calculated with the formula DNI= (neutrophil subgroup + eosinophil subgroup measured in the myeloperoxidase channel) - (polymorphonuclear subgroup

measured in the nuclear lobularity channel), were recorded in accordance with the purpose of the study.

Statistical Analysis

IBM SPSS 16.0 for Windows package program was used for statistical analysis of the study. First, demographic data were analyzed. Normality analyzes of the data were performed using the Shapiro-Wilk test, histogram and Q-plot. Normally distributed data were expressed as mean ± standard deviation, and non-normally distributed data were expressed as median, interquartile range, and min-max. Firstly, univariate analyzes were performed between the two groups, deceased and survivor. Pearson's Chi-Square and Fisher's Exact tests were used for the analysis of categorical variables. In the comparison of two independent groups, the Mann-Whitney-U test was used for non-normally distributed parameters and the Independent Samples-t test was used for normally distributed parameters. In these analyzes, multivariate analysis (logistic regression analysis) was performed with parameters that were statistically significantly different. ROC analysis was performed on the parameters found to be effective on mortality in the multivariate analysis, the areas under the curve were shown, and diagnostic statistics such as specificity-sensitivity for some cut-off values were given. P<0.05 was used for the statistical significance level.

Results

Our study included 311 patients diagnosed with pulmonary embolism in the emergency department. In our study, when the distribution of patients by gender was compared, the female sex ratio was 44.7% (n:139) and the male sex ratio was 55.3% (n:172). The mean age of all cases was 69±17, the median age was 72 (IQR: 59-82), the minimum age of the patients was 21 and the maximum was 97. Considering the 28-day mortality rates, 17.4% (n:54) of the patients died, while 82.6% (n:257) of the patients survived. When the 28-day mortality rate was examined, the median age of the survivor group was 70, and the median age of the deceased group was 76. A statistically significant difference was found when mortality was compared according to age in the statistical analysis performed with the Mann-Whitney-U test. It was determined that patients with older age had a higher mortality rate. The distribution of mortality by age and sex is shown in Table 1.

In our study, considering the patients who were given thrombolytic therapy in the emergency department, 10 % (n:31) of the patients were given thrombolytic therapy. The rate of patients who were hospitalized in the emergency department without thrombolytic therapy or discharged with drug therapy was found to be 90 % (n:280). Of 31 patients who received thrombolytic therapy, 80.6% (n:25) were found to be alive; 19.4% (n:6) of the patients were found to be deceased within 28 days. When the effect on 28-day mortality in the patients who were given and not given thrombolytics in the emergency department were compared, no significant difference was found (p:0.759). Table 2 shows the distribution of mortality according to thrombolytic therapy in the emergency department.

When the biochemical parameters were evaluated according to the presence of 28-day mortality, WBC, NEU, LYM, LYM%, EOS, RBC, HGB, RDW, DNI, urea, D-dimer, Troponin and CRP were found to be statistically significantly different between the two groups, as shown in Table 3. There was a significant difference between the DNI values in the survivor and deceased groups. Median DNI value was 0.00 (0.00-1.33) in the survivor group; 0.20 (0.00-2.90) in the deceased group. The p-value was found to be 0.013.

In our study, DNI, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, body temperature, and SaO2 levels of patients who were given and not given thrombolytics in the emergency room were compared. Heart rate (p<0.001), respiratory rate (p:0.023) and SaO2 levels (p:0.007) of the patients who were given thrombolytics in the emergency department were found to be significant. The effect

Table 1. Mortality distribution according to age and sex

Parameter		28- day Mortality		p
		Survivor Number (%)	Deceased Number (%)	
Sex	Female	112 (80,6)	27 (19,4)	0,388
	Male	145 (84,3)	27 (15,7)	
Age	Median	70 (56-81)	76 (71-87)	0,001*
	Minimum-maximum	21-97	28-94	

Pearson Chi-Square test, *Mann-Whitney-U test

Table 2. Mortality distribution according to the thrombolytic therapy

Parameter		28- Day Mortality		p
		Survivor Number (%)	Deceased Number (%)	
Thrombolytic in Emergency	Not Administered	227 (82,8)	47 (17,2)	0,759
	Administered	25 (80,6)	6 (19,4)	

Table 3. Effect of biochemical parameters on mortality

Parameter	28 Day Mortality		Mann Whitney U test p-value
	Survivor Median (IQR)	Deceased Median (IQR)	
WBC	9,45 (7,06-12,08)	11,22 (8,50-17,48)	<0,001
NEU	6,68 (4,80-9,51)	9,40 (6,58-15,61)	<0,001
LYM	1,32 (1,03-1,81)	0,97 (0,55-1,38)	0,004
LYM%	14,60 (9,25-24,03)	6,90 (4,90-14,80)	<0,001
MONO	0,55 (0,40-0,69)	0,515 (0,37-0,63)	0,212
EOS	0,12 (0,05-0,25)	0,04 (0,02-0,09)	<0,001
BASO	0,02 (0,01-0,04)	0,015 (0,01-0,03)	0,101
RBC*	4,40 ± 0,69 (4,25-4,54)	4,35 ± 0,59 (3,98-4,72)	<0,001*
HGB	12,80 (11,25-14,25)	11,15 (9,78-12,93)	<0,001
PLT	240,00 (184,50-304,25)	259,50 (167,00-317,00)	0,383
RDW	14,60 (13,80-16,23)	14,90 (14,08-16,85)	<0,001
DNI	0,00 (0,00-1,33)	0,20 (0,00-2,90)	0,013
Glucose	112,50 (99,75-153,75)	120,50 (98,25-220,25)	0,082
Urea	41,0 (30-58,5)	66 (37,75-109,75)	<0,001
Creatinine	0,97 (0,78-1,18)	0,675 (0,53-1,12)	0,523
D-dimer	4,46 (2,49-11,73)	6,3 (3,57-11,77)	0,029
pH	7,43 (7,40-7,46)	7,39 (7,35-7,49)	0,711
Lactate	1,39 (1,10-1,86)	1,595 (1,17-2,02)	0,092
CO2	36 (31,43-40,85)	39,65 (31,25-45,20)	0,542
Troponin	55 (13-307,5)	43,5 (12,49-275)	0,012
CRP	15,70 (0,09-59,25)	7,91 (0,17-59,00)	0,025
BNP	879,5 (182-3613)	1083,5 (175-10008,5)	0,084

of DNI level in foreseeing thrombolytic therapy was not found to be significant (p:0.550).

Discussion

In our study, the data of 311 patients who were diagnosed with acute pulmonary embolism at emergency service admission were evaluated. When we look at the patients with pulmonary embolism who receive treatment in our country, the ratio of male and female sexes is equal. In our study, when the distribution of patients by gender was compared, the female sex ratio was 44.7% (n:139) and the male sex ratio was 55.3% (n:172). When we look at the country in general, a slightly higher male sex ratio was found in our study. The risk of venous thromboembolism increases with age. The incidence of venous thromboembolism after the age of 80 is approximately 10 times higher than in patients aged 45-50 years. In our study, in which a total of 311 patients were evaluated, the mean age of all cases was 69±17 years, and the median age of 72 (IQR: 59-82) was close to the country average. The minimum age of the patients was 21, and the maximum was 97. When the 28-day mortality rate was examined, the median age of the survivor group was found to be 70, and the median age of the deceased group was 76. It was determined that patients with older age had a higher mortality rate.

In this study, we showed that DNI is a significant and independent predictor of 28-day mortality in patients with acute PE. We determined that DNI values at emergency service admission could significantly indicate 28-day mortality in this patient group. Therefore, DNI values obtained quickly, easily and inexpensively as part of the complete blood count can be used to evaluate the severity of the disease regardless of hemodynamic instability in patients with acute PE [16]. Age, changes in consciousness, presence of malignancy, systolic and diastolic blood pressures, left ventricular ejection fraction and pulmonary artery pressure, WBC, HGB, DNI, urea, D-dimer, Troponin and CRP are risk factors for 28-day mortality in patients with acute PE. Although many studies have tried to stratify the risk in patients with acute PE, simple and easily available markers are needed to evaluate the prognosis in the emergency setting. Values such as Troponin, D-dimer, and C-reactive protein were found to be significant in terms of mortality in our study. However, it has been understood that these are not statistically superior to DNI. Given the availability and cost-effectiveness of DNI compared to these measurements, DNI may represent a valuable alternative marker for risk stratification in patients with PE.

Given the importance of neutrophils in the pathogenesis of acute PE, few studies have mentioned mechanisms explaining this early and rapid release of immature granulocytes. In patients with upper gastrointestinal bleeding, Kong et al. suggested that massive bleeding at the injured site induces a rapid expansion of circulating neutrophils to compensate for the loss of active neutrophils, preferentially secondary to the massive loss, consumption, and destruction of mature cells [17,18]. Major bleeding or shock is associated with the production of proinflammatory cytokines and chemokines [17,19]. First, in the pathogenesis of acute PE, the hematopoietic system may rapidly transition from steady-state to emergency granulopoiesis to compensate for the secondary loss of active neutrophils resulting from neutrophil infiltration and destruction of mature cells under stress conditions. Increased production of pro-inflammatory cytokines and chemokines (such as interleukin [IL]-6, IL-8, and tumor necrosis factor-alpha) causes rapid expansion of neutrophils immediately after PE. This exacerbates the local and systemic inflammatory response. At the same time, severe systemic and sterile inflammation can cause microvascular dysfunction, tissue damage, and dysregulation of metabolism [19]. Second, widespread inflammation requires profound "compensatory" down-regulation of immune responses. Neutrophil paralysis, known as dysregulated neutrophil function, reduces tissue damage in severe sterile inflammation as a result of impaired migration of neutrophils to the damaged area and neutrophil sequestration in end organs. As a result, the number of circulating immature granulocytes may increase to compensate for the rapid decrease in active neutrophil count. Under these conditions, the host is highly susceptible to infections. In addition, dysregulation of immune mechanisms may increase mortality [20,21]. Third, sustained hypotension and shock as a result of RV failure are significantly associated with higher mortality in patients with acute PE; therefore, urgent reperfusion therapy is needed [22]. In particular, hemodynamic instability or severe inflammation may affect critical regulatory mechanisms for neutrophil release from the bone marrow, due to an increase in the severity of acute PE. According to the results of our study, considering the relationship between this value and 28-day mortality, it shows that if the DNI value increases, patients with acute PE should be followed carefully.

In our study, we found that high DNI was an important independent risk factor for 28-day mortality. Therefore, we recommend applying these DNI values, which can be determined quickly, easily and inexpensively, to evaluate the severity of such patients at the time of reporting to the emergency room and, if necessary, after 24 hours. Acute PE is a critical condition that usually leads to death soon after admission in the emergency room. Risk stratification should be done immediately in the emergency room [7]. Kim et al. [16] revealed that DNI >4.9% at emergency room admission, >4.9% on day 1, and >2.5% on day 2 were associated with a 28-day risk of mortality in patients with acute cholangitis. Taeyoung Kong et al. found that changes in DNI values in patients with pulmonary embolism were associated with poor clinical outcomes on 28-day mortality [22]. Similar results were found in our study.

In the first 24 hours after admission in the ICU, DNI >6.5% was a useful diagnostic marker for severe sepsis and septic shock [23]. Similarly, in patients with recovery of spontaneous circulation after out-of-hospital cardiac arrest, DNI was able to reflect damage associated inflammation. It has also been shown to reflect the severity of systemic and sterile inflammation as seen in patients with hemorrhagic shock. Yune et al. reported that DNI values of >8.4% (HR, 3.23) at admission and >10.5% at day 1 (HR, 3.29) were significantly associated with 30-day mortality in survivors of out-of-hospital cardiac arrest [24]. Similarly, from our study results, we suggest that DNI has similar clinical outcomes in patients with acute PE and supports its use in risk stratification of these patients.

The actual processes and mechanisms by which immature

granulocytes affect the pathophysiology of clinical deterioration in patients with acute PE still need to be elucidated. Therefore, more in-depth studies are needed to confirm the clinical usefulness of DNI as a prognostic marker in patients with acute PE.

Conclusion

The DNI value, reflecting the fraction of circulating immature granulocytes obtained as part of the complete blood count, can be easily determined without additional cost or time burden. As a result of our study, we suggest the use of DNI value as a guide and useful to predict the risk of early 28-day mortality in patients with acute PE and to determine the treatment strategy.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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